Bioethics of Off-Label Prescriptions

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Off-Label prescribing also known as “unapproved use” is the physicians practice of prescribing a drug or a medical device for a purpose different from one of the indications for which the product is approved by the Food and Drug Administration (FDA). This practice is widespread and it is estimated that nearly 60% of drug prescriptions per year are for off-label indications. Some common off-label drug uses include 1) treating a disease other than the one for which the drug is approved for, 2) giving a drug at a different dose or frequency than it's been approved for and 3) using a drug to treat children when its approval is limited to adults.

Real concerns about unexpected safety issue of drugs surfaced for the first time in 1962 closely following the “Thalidomide tragedy” where use of this drug, approved as a sedative, and marketed by Chemie Greunthral resulted in the birth of several thousand malformed babies to mothers who had taken this drug for hyper emesis during the first trimester of pregnancy. Amendments were made in the drug laws which made it mandatory for all new drugs to pass through ever so stringent testing for drug toxicity, safety and efficacy before they are even taken up for their first use in clinical trial on humans.

In Ophthalmic practice, off-label prescription of approved drugs include 1) Intravitreal injection of antibiotics, 2) Use of mitomycin-C and 5 Fluorouracil, 3) Periocular injection and intraocular administration of steroids, 4) Use of immunosuppressive for uveitis, 5) Use of photodynamic therapy for non AMD lesions, 6) Intravitreal injection of Bevacizumab (avastin), and 7) use of tissue plasminogen activator.

The IND (Investigational New Drug Application) for clinical trial stipulates restriction of the trials for specific age groups leaving out pediatric (below 12 years), women in the reproductive phase (17-45 years), lactating mothers, and, even geriatric patients (60 years and above). Consequently when the drug goes for approval its use will be initially restricted to patients belonging to the class and type on which clinical trials have been completed and the drug was found to the safe and effective for the indication for which the drug was tested.

What is good for the goose may not be good for the gosling! Extension of its use to the pediatric and other population would be possible only after the drug has been tested for such population in specially conducted trials which in many cases may take a couple of years more after the first approval. In practice until use in these population is approved, no claim can be made on the safety and efficacy of the drug in such population.

Development of pediatric indications for potentially beneficial off-label drugs has led to investigations and publishing of several studies to establish safe dosing guidelines for many off-label drugs that are now considered ‘standard-of-care’ in infants and children. Publication of well documented small case series in peer reviewed journals indicate that high quality evidence can and does exist beyond federally sanctioned approval and may be used to deliver safe and effective drug as well as expunge those that may be dangerous from the market.

All these parameters change when the same drug is administrated for a new indication for which no data has been generated. Thus the treatment schedules, the dosages, and duration of treatment in off-label use could
be very different from the approved schedules and such ad-hoc approaches could result in serious adverse reaction or may have even fatal outcomes. Testing for a new indication calls for fresh clinical trials and sometimes even repetition of toxicology studies to ensure that the doses used for the new indication does not result in toxic manifestations and adverse drug reactions.

As a corollary to this, such use cannot be indicated in labels and product literature, but also cannot be promoted directly or indirectly by the manufacturer or the distributor, to the medical profession.

From a legal and ethical standpoint, off-label use represents a delicate balance between the regulatory objective of protecting patients from unsafe or ineffective drugs and medical devices on the one hand, and the prerogative of physicians to use their professional judgment in treating patients on the other.

The practice of off-label drug prescriptions raises a number of legal and ethical issues. To state a few 1) Is off-label prescription a form of a human experimentation? 2) Could a failure to prescribe off-label medications leave the physician vulnerable to a malpractice suit? 3) Does the physician have a duty to inform the patient that the product is being prescribed off-label? 4) In prescribing a drug for an unapproved use, does the physician act as a ‘learned intermediary’, thereby relieving the drug manufacturer of liability for resulting patient harm? 5) How does the FDA regulate off-label prescribing? 6) Can a manufacturer promote a product for an off-label use?

In the world of law, where matters are rarely clear cut, there are few certainties about off-label use. First it does not violate FDA law. The agency itself acknowledges this and its centre for drug evaluation states that “Neither the FDA nor the federal government regulate the practice of medicine. Any approved product may be used by a licensed practitioner for uses other than those stated in the product label”.

The pace of medical discovery runs ahead of the FDA’s regulatory machinery and hence the off-label use of some drugs is frequently considered as ‘state-of-the-art’ treatment and in some circumstances an off-label use of a particular drug or device may even define the standard of care. However this doesn’t mean that a physician should feel free to use a product off-label in the same way that he or she might employ the product for one of its approved indication. The physician lacks information on its use, dosage, and route of administration. Furthermore the safety and efficacy for the unapproved use may not have been established by adequate and well controlled clinical trials. Clearly, anecdotal data does not take the place of such investigations and the fact that the product has been proven safe and efficacious for one use does not mean that it is safe and efficacious for any other. Given the risk of liability for using a product for an unapproved purpose, physicians should do so only when they are convinced that the unapproved status of use is outweighed by the potential benefit to the patient. Often this will be obvious for example, when there are no other available products, such as is the case with many drugs prescribed for children, which until recently were rarely tested in that population.

Is off-label use a form of human experimentation? A clear cut distinction rarely exist between research and therapy and the main key for this distinction is the physician’s intent. If the intent is primarily to benefit the patient the intervention is therapy. If the intervention is solely to test a hypothesis and obtain generalizable knowledge, the intervention is an experiment. Yet in employing a product for an unapproved use the physician often has both objectives in mind. She hopes to benefit her patients, and also hopes to find out whether this intervention can help similar patients. The distinction becomes even more blurred if the physician has a strong financial interest in the success of the intervention.

Should manufacturers be permitted to promote goods for unapproved uses? Off-label promotion makes more information available to the physicians, enabling them to make better treatment recommendations for patients. It allows manufacturers to avoid or postpone the cost of obtaining FDA approval so that they can make products available more quickly and invest more in research and development. Off-label promotion especially benefits patients with orphan diseases, who often must rely on off-label uses for treatment. On the other hand it undercuts the FDA’s ability to ensure safety and efficacy and removes incentives for manufacturers to conduct studies on
safety and efficacy and encourages them to seek FDA approval for the narrowest, most “easy-to-support” indications.

The doctrine of informed consent obliges physician to provide patients with material information about proposed treatments, alternatives the potential risk and expected benefits of each. An informed consent will safeguard both physician and patients especially when the proposed line of therapy involves off-label use of medicine or device. The ophthalmic community has a tremendous responsibility to demonstrate safety and efficacy of off-label drugs by providing adequate supporting data via peer reviewed publication. The treating physician should document in the chart details of the decision-making process including previous treatment and diagnostic studies, dose and lot number of the drug, as well as the discharge and follow up instructions. Use a drug specific informed consent (e.g. for Avastin; a drug specific informed consent can be downloaded from www.omic.com) and discuss the off-label status of the drug, making sure that the patient has adequate time to take a decision before signing the informed consent form. Discuss clearly the off-label status, the attendant risks as well as why the FDA approved options have not been considered. Failure to provide or at least discuss off-label therapy if it is the standard of care may make the physician liable to a malpractice suite. —— Damned if you do! Damned if you do not!

The question of reimbursement! Some insurance companies will not cover the cost of a drug – most often if it is a costly drug and if it is prescribed for off-label use. The doctor can prove through the use of peer reviewed medical studies or other reliable information that the off-label application is appropriate – that should bolster the case in getting reimbursement.

FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if the carrier determines the use to the medically accepted, taking into consideration authoritative medical literature and or accepted standard of medical practices.

Clearly off-label use of drugs by individual physicians is legal and leads to new therapeutic advances. A clever clinician putting together inferences from pathophysiology of diseases and the known pharmacological properties of approved agents may accumulate data on efficacy and toxicity in new settings.

The FDA encourages the off-label use of drugs with the implied commitment to the profession to do the necessary clinical research to gain approved labeling for the new indication. The fact that the drug is already approved bypasses the regulatory maze necessary for a physician to try these agents. While the manufacturer cannot advertise the off-label use of a drug they have the responsibility to file an IND application with the FDA. Individual physicians interacting with their patients should give thought to the benefits of off-label drug use based on pathophysiology and therapeutic logic and side effects in that individual patient. The physician does not require an IND application or review by the Institutional review board, however records should be maintained with the goal of accumulating information that could form the basis of pilot studies that ultimately should lead to expanded indications for the already approved drug. Many of the off-label use of a drug are described and reported as case reports which alert other physician to the possibilities of using these drugs in other patients. With appropriate transparency to the medical community and the patient, these types of small prospective studies will hopefully pave the way for more effective therapies for diseases that has been therapeutically problematic to date.

Use of intravitreal triamcinolone acetonide and anti VEGF, a form of anti angiogenic therapy is on the horizon for aggressive posterior retinopathy of prematurity (AP –ROP) which develops in profoundly immature neonates. The rationale of the therapy with off-label drugs, is the accepted fact that VEGF promotes retinal vascularisation. The BLOCK-ROP study, a phase I trial is underway to study their challenges. Let us wait for conclusive results before experimenting on the vulnerable target population of precious immature neonates in the interim period, and even the AAO advocates exercise of caution in the use of Anti VEGF drugs outside a clinical trial in premature neonates

References


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